REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow. This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

I. Introduction

In the specification, paragraphs are amended on pages 3, 7 and 9 and claims 1, 2, 6, 11, 12 and 17 are amended by clarifying that the crude drug is a mixture, as described on page 9, lines 32-36 of the specification. Claims 21-30 are being added. Independent claim 21 is written in means plus function format of 35 USC 112, paragraph 6 and incorporates the limitations from original claims 1, 10, 11 and 20. The term "means" in claim 21 corresponds to any suitable solid preparation, such as a capsule, tablet or powder, as well as any matrix base or coating and their equivalents which can deliver the active ingredient to a diabetic, as described on page 7, lines 30-35 and page 8, lines 12-15 of the specification. Independent claim 26 incorporates the limitations from original claims 1, 8, 11 and 18. No new matter was added.

After amending the claims as set forth above, claims 1-30 are now pending in this application. Non-elected claims 9, 10, 19 and 20 are withdrawn from consideration.

II. 35 USC 112, Para. 2 Rejections Should Be Withdrawn

Claims 1-8 and 11-18 have been rejected under section 112, paragraph 2 as being indefinite because the scope of the term "crude drug" is unclear. This rejection is respectfully traversed.

The term "crude drug" is a well known term in the art which means a material made of plants, animals and/or minerals, etc., or made by cutting, crushing or drying plants, animals

and/or minerals without changing the nature thereof. For example, crude drugs are widely used as a raw material for Chinese medicine or folk medicine.

Applicants enclose herewith an Appendix which lists scientific articles which use the term "crude drug" in the title and/or abstract. Applicants also note that the JP 11-130,686 reference used in the Office Action also uses the term crude drug in line 2 of paragraph [0017]. Thus, applicants submit that the term "crude drug" has a well established meaning in the art.

If the examiner finds that the above description of the term is not sufficient, then applicants are willing to delete the term "crude" from the claims in order to overcome this rejection.

III. Prior Art Rejections Should Be Withdrawn

Claims 1-5, 7 and 11-16 are rejected under section 102(b) as being anticipated by JP 11-130,686 ("JP '686"). Claims 1, 5, 6, 11, 15 and 16 are rejected under section 103(a) as being obvious over JP '686. Claims 1, 8, 11 and 18 are rejected under section 103(a) as being obvious over JP '686 in view of U.S. 6, 200,998 ("US '998"). These rejections are respectfully traversed.

A. 102(b) Rejection

Claim 1 has been amended to recite a side-effect reducing agent which is dosed for relieving a side effect of thiazolidine compounds. Claim 11 has been amended to recite a hypoglycemic effect enhancer which is dosed for enhancing hypoglycemic effect of thiazolidine compounds. JP '686 does not teach or suggest these limitations.

JP '686 discloses an agent comprising Bofu-tsusho-san together with a plantago seed and mulukhiya, and optionally a red pepper and/or rhei rhizome. The agent has enhanced anti-obesity effect of Bofu-tsusho-san by using a plantago seed and others. However, this reference does not disclose relieving a side effect of thiazolidine compounds or enhancing hypoglycemic effect of thiazolidine compounds. Thus, the agent of JP '686 is not dosed for

relieving a side effect of thiazolidine compounds or for enhancing hypoglycemic effect of thiazolidine compounds, as recited in claims 1 and 11, respectively, of the present application. Therefore, JP '686 does not anticipate claims 1 and 11 because JP '686 does not teach every element of claims 1 and 11.

B. 103(a) Rejection Over JP '686

JP '686 discloses amounts of Bofu-tsusho-san and a plantago seed and other ingredients. The amounts of the ingredients are selected from the viewpoint of enhancing an anti-obesity effect of Bofu-tsusho-san. JP '686 does not describe selecting amounts of Ephedrae Herba, Glycyrrhizae Radix and Gypsum Fibrosum for relieving a side effect of thiazolidine compounds or for enhancing hypoglycemic effect of thiazolidine compounds. Thus, the present claims are not obvious over JP '686 because JP '686 does not teach or suggest that an agent having an anti-obesity effect has the above effects with respect to the thiazolidine compounds without carrying out tests described in the working examples of the present specification.

C. 103(a) Rejection Over JP '686 and US '998

Claims 8 and 18 and new independent claim 26 recite using the crude drug mixture together with a thiazolidine compound. This is not taught or suggested by either JP '686 or US '998. Furthermore, the claimed composition provides unexpected results compared to the prior art compositions.

1. Prior Art Does Not Teach Claimed Invention

JP '686 discloses that Bofu-tsusho-san is effective for anti-obesity, but is silent about Bofu-tsusho-san being effective for body weight gain induced by pioglitazone and acting as a hypoglycemic effect enhancer for pioglitazone.

US '998 discloses the method of treating diabetes by administering a composition comprising pioglitazone. US '998 also discloses in col. 15, lines 54-57 the use of various

anti-obesity compounds including fenfluramine, orlistat, etc. in combination with pioglitazone.

However, US '998 does not teach or suggest using a crude drug mixture, such as Bofu-tsusho-san, together with pioglitazone. The listed anti-obesity compounds in US '998 are quite different from the claimed crude drug mixture, such as Bofu-tsusho-san, and would not motivate one of ordinary skill in the art to substitute them with the claimed crude drug mixture, such as Bofu-tsusho-san. Thus, one of ordinary skill in the art would not be motivated to combine a crude drug mixture, such as Bofu-tsusho-san, of JP '686 together with pioglitazone of US '998.

Furthermore, US '998 does not specifically state that the purpose of using the above anti-obesity compounds is to suppress body weight gain induced by pioglitazone compounds and to enhance the hypoglycemic effect of pioglitazone. Thus, US '998 does not teach or suggest dosing the anti-obesity compound for relieving a side effect of thiazolidine compounds or for enhancing hypoglycemic effect of thiazolidine compounds, as recited in claims 1 and 11, respectively, of the present application. Applicants respectfully request that the 103(a) rejection be withdrawn.

2. Unexpected Results

As described in the specification of the present application, body weight gain and body fat gain have often been observed by long-term administration of a thiazolidine compound, such as pioglitazone, which reduces the hypoglycemic effect of the thiazolidine compound (J. Japan Diab. Soc., vol 44, No. 4, pp. 323-327, 2001).

As noted on the bottom of page 2 of the present application, 3-Guanidinopropionic acid and voglibose are known as drugs which suppress body weight gain induced by pioglitazone. However, the duration of administration of the above drugs and pioglitazone in combination was only 2 weeks in both studies, and it has not been elucidated whether the above drugs control body weight gain under long-term administration.

In contrast, the claimed crude drug mixture, when used in combination with thiazolidine compounds, relieves a side effect of thiazolidine compounds and enhances hypoglycemic effect of thiazolidine compounds over a long period. These results are described in the examples on pages 10-19. The examples show that the positive effects of the crude drug mixture last for at least 4-5 weeks.

These results are unexpected from the prior art applied in the Office Action. Thus, even if there was motivation to combine the prior art references as suggested in the Office Action to establish a *prima facie* case of obviousness, then the unexpected results are sufficient to rebut this *prima facie* case.

D. Claim 21

Claim 21 recites a means for providing the crude drug mixture to a diabetic concomitantly with, or before or after administration of a thiazolidine compound to the diabetic for at least one of relieving a side effect induced by the thiazolidine compound or enhancing a hypoglycemic effects of the thiazolidine compound. This claim element is written in means plus function form of 35 USC 112, paragraph 6.

In order to establish a *prima facie* case of unpatentability of a claim containing a § 112, ¶ 6 "means plus function" element, the Office Action must cite a prior art element that actually performs the claimed function. It is not enough that the prior art's structure is capable of performing the claimed function when the prior art specifically teaches against performing such a function. *See* MPEP § 2183. For example, the predecessor court to the Federal Circuit stated:

> We cannot agree with the board that the [means plus function] claims "merely recite 'a means'." They recite a means plus a function which is not to be found in Leutwyler [the prior art reference]. They therefore do not read on that reference and are not anticipated thereby.

In re Mott, 194 USPQ 305, 307 (CCPA 1977). The Federal Circuit cited *In re Mott* with approval in *RCA Corp. v. Applied Digital Data Systems, Inc.*, 221 USPQ 385 (Fed. Cir. 1984). On page 389, footnote 5, of the *RCA* decision, the Federal Circuit stated:

> The claims here define the invention in terms of specific "means-plus-function" elements. The limitations which must be met by an anticipatory reference are those set forth in each statement of function. In re Mott, 557 F.2d 266, 269, 194 USPQ 305, 307 (CCPA 1977). Such a limitation cannot be met by an element in a reference that performs a different function, even though it may be part of a device embodying the same general overall concept. [emphasis added].

The Office Action cannot focus only on the structure of the prior art and selectively ignore how it functions in the context of that prior art. The reference as a whole must be considered. Thus, the function in means plus function claim elements is a positive claim limitation that must be given patentable weight.

In case of claim 21, the function of "providing the crude drug mixture to a diabetic concomitantly with, or before or after administration of a thiazolidine compound to the diabetic for at least one of relieving the side effect induced by a thiazolidine compound or enhancing a hypoglycemic effects of the thiazolidine compound" must be given patentable weight.

Since JP '686 and US '998 do not teach or suggest this function, claim 21 is considered to be in condition for allowance. Furthermore, applicants incorporate by reference the argument from the prior section that there is no motivation to combine JP '686 and US '998 to arrive at the composition of claim 21.

IV. Conclusion

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

Date 11/2/05

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The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Reference

1. Kohno, H., Maeda, M., Tanino, M., Tsukio, Y., Ueda, N., Wada, K., Sugie, S., Mori, H., Tanaka, T. : A bitter diterpenoid furanolactone columbin from Calumbae Radix inhibits azoxymethane-induced rat colon carcinogenesis. Cancer Lett. 2002 Sep 26;183(2):131-9.

[Abstract]

The modifying effect of dietary administration of a diterpenoid furanolactone columbin isolated from the crude drug Calumbae Radix (the root of Jateorhiza columba MIERS, Menispermacea) on azoxymethane (AOM)-induced was investigated in male F344 rats. Animals were initiated with AOM (three weekly subcutaneous injections of 15 mg/kg body weight) to induce colonic neoplasms. They were fed the experimental diets mixed with columbin (4, 20, and 100 ppm) for 4 weeks, starting 1 week before the first dosing of AOM and thereafter maintained on the basal diet without columbin. Additional experimental groups included the AOM alone group, the columbin alone group (100 ppm in diet for 4 weeks), and the untreated control group. Dietary feeding of columbin (4, 20, and 100 ppm) during the initiation phase of AOM-induced colon carcinogenesis reduced the incidence and multiplicity of colonic adenocarcinoma and the inhibition by feeding of 20 ppm (incidence: 20%, P=0.0242 and multiplicity: 0.20+/-0.40, P<0.02) and 100 ppm (incidence: 10%, P=0.0029 and multiplicity: 0.10+/-0.30, P<0.002) columbin was significant when compared with the AOM alone group (incidence: 55% and multiplicity: 0.55+/-0.50). Also, columbin administration in diet lowered the number of argyrophilic nucleolar organizer regions protein per nucleus in non-lesional colonic crypts and the blood polyamine content, which are reflected in cell proliferation activity. These results indicate chemopreventive ability of dietary columbin against chemically induced colon tumorigenesis when fed during the initiation phase, providing a scientific basis for chemopreventive ability of columbin against human colon cancer.

2. Tadano, T., Nakagawasai, O., Niijima, F., Tan-no, K., Hanawa, M.A., Sakata, Y., Sutoo, D., Nemoto, Y., Ida, Y., Endo, Y.: Effect of nutritive and tonic crude drugs on physical fatigue-induced stress models in mice. Pharmacol Res. 2003 Mar;47(3):195-9.

[Abstract]

The present study was undertaken to investigate the acute anti-fatigue effect of a liquid nutritive and tonic crude drugs (NTDs) on stress induced in mice. After forced walking for 3 or 6h, the NTDs (applied orally, 10 ml/kg) significantly increased locomotor activity, while the administration of NTDs after rapid eye movement (REM) sleep deprivation stress and after immobilization stress did not show a specific effect, having a similar effect as the vehicle with added vitamins, taurine and caffeine. The administration of NTDs after freezing due to electric shock stress showed a specific effect which was not seen in other control groups, water, vehicle (ethanol) and vehicle including vitamins, taurine and caffeine and so resemble the specific effect of NTDs in the stress of forced walking. The present results indicate that the NTDs produced an anti-fatigue effect on the decreased locomotor activity after forced walking and immobility induced by electric stimulation. However, the crude drugs were not effective in improving immobility after sleep deprivation or immobilization stress.

3. Yokozawa, T., Kim, H.Y., Yamabe, N.: Amelioration of diabetic nephropathy by dried Rehmanniae Radix (Di Huang) extract. Am J Chin Med. 2004;32(6):829-39.

[Abstract]

The effects of dried Rehmanniae Radix (Di Huang) extract were investigated using a diabetic nephropathy model: rats given streptozotocin after nephrectomy. The results showed that this crude drug reduced the magnitudes of the increases in glucose, urea nitrogen, 5-hydroxymethylfurfural and thiobarbituric acid (TBA)-reactive substance levels, with the effects being most marked in the high blood glucose group. The renal histopathological lesions, which were conspicuous in rats not given dried Rehmanniae Radix extract, were ameliorated considerably in the high blood glucose group given this extract. It appears that dried Rehmanniae

Radix extract may be useful as a therapeutic agent for inhibiting the progression of diabetic nephropathy. On the basis of these results, the possible mechanisms of action of this crude drug are discussed.

4. Loungratana, P., Tanaka, H., Shoyama, Y.: Production of monoclonal antibody against ginkgolic acids in Ginkgo biloba Linn. Am J Chin Med. 2004;32(1):33-48.

[Abstract]

A competitive enzyme-linked immunosorbent assay (ELISA) for ginkgolic acids (GAs) was developed using monoclonal antibody (MAb) 9F raised against 6-(13-formylheptyl) salicylic acid covalently coupled to bovine serum albumin (BSA). ELISA, at an effective measuring range of 300 ng/ml-1 microgram/ml of GA15:1, was successful in detecting GAs content in ginkgo leaves and standardized extracts due to the lack of cross-reactivity against various related compounds. The sensitive and simple immunoassay developed in this study was validated to be specific for the quantitative determination of total Gas content in ginkgo crude drugs with no interference from the sample matrix. The analytical recovery of spiked GA15:1 was 103% in a concentration range between 10 and 40 mg/g dry weight of ginkgo leaves.

5. Maurya, R., Singh, R., Deepak, M., Handa, S.S., Yadav, P.P., Mishra, P.K.: Constituents of Pterocarpus marsupium: an ayurvedic crude drug. Phytochemistry. 2004 Apr;65(7):915-20.

[Abstract]

Five new flavonoid C-glucosides, 6-hydroxy-2-(4-hydroxybenzyl)-benzofuran-7-C-beta-d-glucopyranoside (1), 3-(alpha-methoxy-4-hydroxybenzylidene)-6-hydroxybenzo-2(3H)-furanone-7-C-beta-d- glucopyranoside (2), 2-hydroxy-2-p-hydroxybenzyl-3(2H)-6-hydroxybenzofuranone-7-C-beta-d-glucopyranos ide (4), 8-(C-beta-d-glucopyranosyl)-7,3',4'-trihydroxyflavone (5) and 1,2-bis(2,4-dihydroxy,3-C-glucopyranosyl)-ethanedione (6) and two known compounds C-beta-d-glucopyranosyl-2,6-dihydroxyl benzene (7) and sesquiterpene (8), were isolated from an aqueous extract of the heartwood of Pterocarpus marsupium. The structure has been established using spectroscopic data.

6. Kletter, C., Glasl, S., Presser, A., Werner, L, Reznicek, G., Narantuya, S., Cellck, S., aslinger, E., Jurenitsch, J.: Morphological, chemical and functional analysis of catuaba preparations. Planta Med. 2004 Oct;70(10):993-1000.

[Abstract]

Fourteen commercial samples of the popular Brazilian aphrodisiac Catuaba specified as bark drugs of Anemopaegma, Erythroxylum and Trichilia species were examined for identity and purity. Only a minority of the examined Catuaba samples contained the crude drugs claimed on the labels. More than half of the products were adulterated with different crude drugs. The majority of the samples contained a bark originating from Trichilia catigua. The TLC fingerprints confirmed the heterogeneity, in 50% of the samples tropane alkaloids of various concentrations were detected. TLC and HPLC methods for separation and identification of the tropane alkaloids were developed and their analytical data (RF values, retention times, ESI-MS) given. The structure elucidation of the two main alkaloids, catuabine D and its hydroxymethyl derivative, is presented. The 1H- and 13C-NMR assignments of these alkaloids are discussed with regard to literature data. Neither aqueous nor methanolic extracts of the Trichilia catigua reference material nor alkaloid-enriched fractions of commercial samples showed any effect on the rabbit corpus cavernosum in an in vitro test.